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REVIEW ARTICLE

Beneficial effects of ezetimibe-based therapy in patients with dyslipidemia

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Summary Treatment of dyslipidemia is important for the primary and secondary prevention of cardiovascular events. Although statins induce the intensive lowering of low-density lipoprotein (LDL) cholesterol levels, two-thirds of cardiovascular events are not prevented. Ezetimibe has been shown to be a selective inhibitor of the Niemann-Pick C1-like 1 (NPC1L1) transporter of cholesterol across the intestinal wall. Ezetimibe-based therapy may hold the promise of more intensive lowering of LDL cholesterol. This review will address the beneficial effects of ezetimibe in patients with dyslipidemia.

Contents

Introduction

Ezetimibe (1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxypropyl]-(4S)-(4-hydroxypropyl)-2-azetidinone) is a potent inhibitor of cholesterol and phytosterol uptake [1]. Since low cholesterol absorption has been associated with

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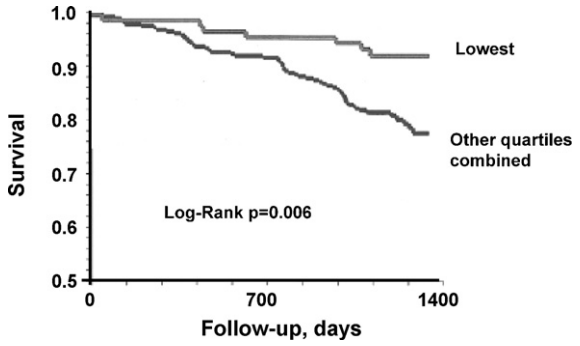

Figure 1 Unadjusted Kaplan—Meier curve for total mortality in the lowest quartile of serum cholestanol-to-cholesterol ratio ($n = 94$) vs. other quartiles combined ($n = 284$).

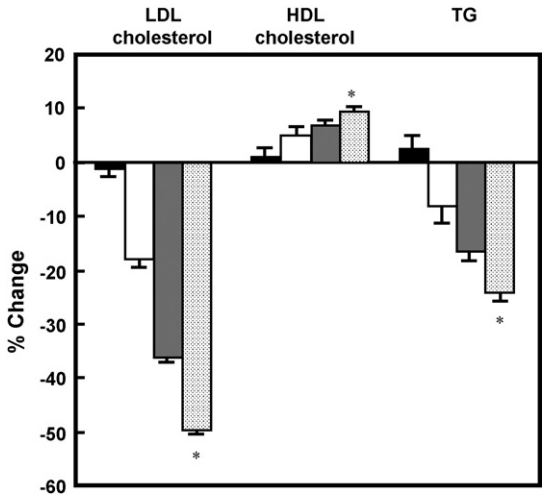

Figure 3 Changes in serum lipid profile in placebo ($n = 70$, black bars), ezetimibe therapy ($n = 61$, white bars), simvastatin therapy ($n = 263$, gray bars), and ezetimibe + simvastatin therapy ($n = 274$, dotted bars) in patients with primary hypercholesterolemia. LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride. *$p < 0.05$ vs. simvastatin therapy.

a lower rate of total mortality [2] (Fig. 1), pharmacological intervention through the inhibition of intestinal cholesterol absorption may be a useful strategy for treating patients with dyslipidemia and/or cardiovascular disease. Niemann-Pick C1-like 1 (NPC1L1) has recently been identified, and has been shown to have features of a plasma membrane transporter, including a secretion signal, 13 predicted transmembrane domains, extensive N-linked glycosylation sites and a sterol-sensing domain [3] (Fig. 2). It is highly expressed on the surface of absorptive jejunal enterocytes. NPC1L1 has been shown to be a direct target of ezetimibe, and an ezetimibe-sensitive pathway plays a role in intestinal cholesterol absorption [4]. Despite the availability of statins, many patients do not achieve lipid targets. Combination therapy with statins and ezetimibe that act via a complementary pathway may allow additional patients to achieve their recommended cholesterol goals. These findings represent an exciting new area in the treatment of dyslipidemia. Ezetimibe-based therapy may hold the promise of more intensive lowering of low-density lipoprotein (LDL) cholesterol. This review will address the beneficial effects of ezetimibe in patients with dyslipidemia.

Ezetimibe monotherapy

Ezetimibe can effectively lower plasma LDL cholesterol to decrease cholesterol absorption [5]. Ezetimibe at 10 mg/day induced an about 20% reduction in LDL cholesterol [6] (Fig. 3). In addition, ezetimibe decreased triglyceride (TG) by about 8% and increased high-density lipoprotein (HDL) cholesterol by about 5%. In patients with primary dyslipidemias, ezetimibe (10 mg/day)

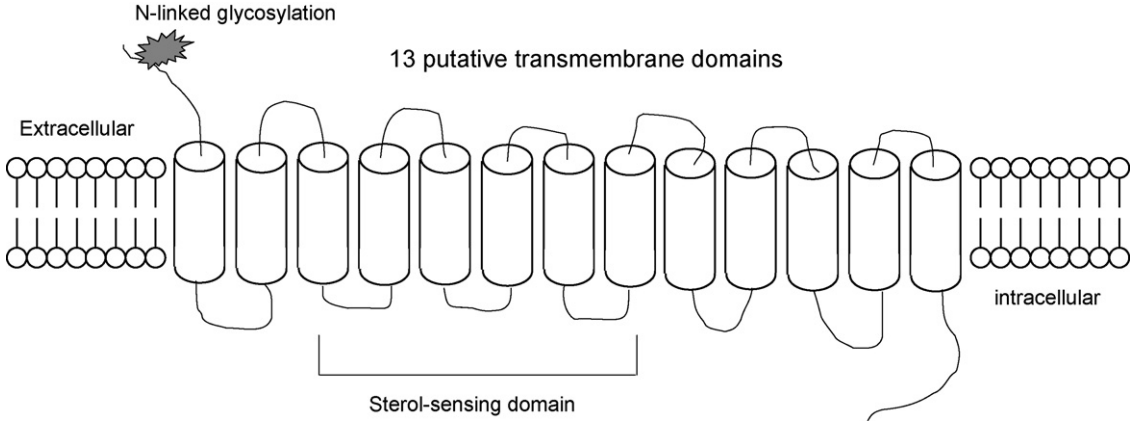

Figure 2 Secondary structure of NPC1L1.

therapy for 16 weeks reduced total, LDL and non-HDL cholesterol values as well as apolipoprotein B concentrations [7]. Patients with TG values >150 mg/dL had significantly greater reductions in the concentrations of small, dense LDL particles compared to those with normal TG levels (49% vs. 19%, respectively; $p < 0.05$). With respect to individual LDL subfractions, cholesterol was significantly reduced by ezetimibe in cholesterol in nearly all LDL subfractions [8]. These results indicate that ezetimibe significantly reduces LDL cholesterol by inhibiting the reabsorption of biliary cholesterol.

Ezetimibe/statin combination therapy

The combination of ezetimibe and statin therapy may synergistically decrease cholesterol absorption and synthesis, since the effective inhibition of cholesterol synthesis and the subsequent reduction in serum cholesterol levels by statins lead to increases in serum plant-sterol levels, probably as a result of reduced biliary secretion and the enhanced absorption of these sterols [9].

In 769 patients with hypercholesterolemia, ongoing statin therapy plus ezetimibe led to significant changes in LDL cholesterol (of −25.1%) (HDL cholesterol +2.7%; TG −14.0%) compared to the results with placebo (LDL cholesterol −3.7%, HDL cholesterol +1.0%, and TG −2.9%) [10]. Among patients who were not at their LDL cholesterol target, 71.5% of those who received statin plus ezetimibe vs. 18.9% of those who received statin plus placebo reached their target levels at the end-point. In multicenter, randomized, double-blind, placebo-controlled studies, an ezetimibe + simvastatin group showed significantly improved LDL cholesterol, HDL cholesterol, and TG compared to a simvastatin-alone group. Ezetimibe plus simvastatin provided an incremental 13.8% LDL cholesterol decrease, 2.4% HDL cholesterol increase, and 7.5% TG decrease compared to simvastatin alone (Fig. 3) [6]. We also performed the Fluvastatin Add-On to Ezetimibe Trial (FAET) in patients with hypercholesterolemia (Fig. 4). After 6 months of ezetimibe monotherapy (10 mg/day), plasma LDL cholesterol decreased by 40 mg/dl (mean: 175−135 mg/dl at 6 months). Ezetimibe plus low-dose of fluvastatin (20 mg/day) combination therapy was started in poor-responders (LDL cholesterol: 158 ± 4 mg/dl after 6 months ezetimibe monotherapy), then the LDL cholesterol levels reduced to 130 ± 4 mg/dl (−28 mg/dl), while LDL cholesterol in ezetimibe monotherapy group (responders) was 128 ± 4 mg/dl. No adverse effect was observed. Although coadministration of ezetimibe plus low-dose of fluvastatin was more effective in reducing plasma concentrations of LDL-C than ezetimibe alone, we need to analyze the patient's characteristics of poor-responder to ezetimibe.

Combination therapy with 10 mg/day ezetimibe and 10 mg/day atorvastatin for 8 weeks

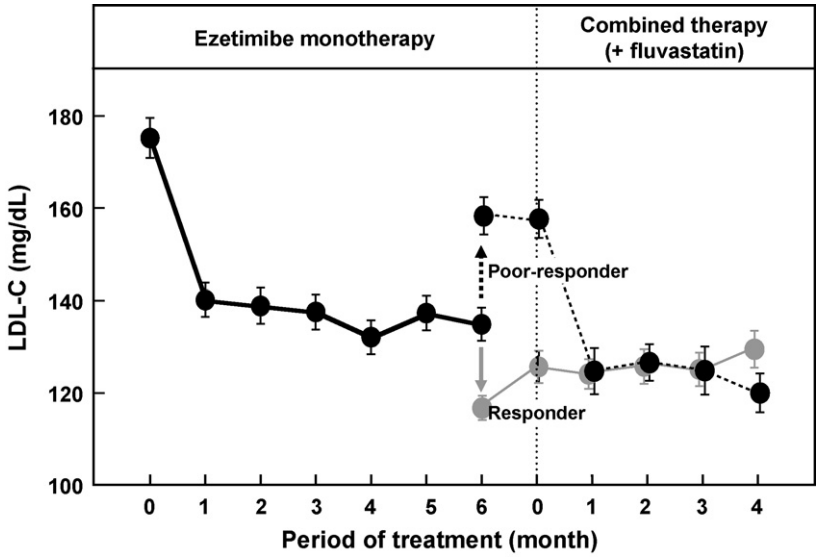

Figure 4 Changes in serum LDL cholesterol levels in patients with hypercholesterolemia ($n = 59$) (Fluvastatin Add-On to Ezetimibe Trial). After 6 months of ezetimibe monotherapy (solid line), combination therapy (ezetimibe + fluvastatin, dotted line) was started in poor-responders ($n = 26$) after 6 months ezetimibe monotherapy. Responders ($n = 33$) continued ezetimibe monotherapy (gray line).

resulted in significantly decreased total serum cholesterol and TG compared to 40 mg/day atorvastatin alone [11]. Ezetimibe/atorvastatin therapy significantly improved LDL cholesterol, HDL cholesterol, TG and high-sensitivity C-reactive protein (hs-CRP) compared to atorvastatin alone [12]. The addition of ezetimibe to on-going simvastatin treatment also resulted in a significantly greater percent reduction in LDL cholesterol from baseline (25.2%) compared to the results with placebo (0.9%). In a double-blind, multicenter, 6-week, parallel-group study, hypercholesterolemic patients were randomized to receive ezetimibe/simvastatin or rosuvastatin. At all doses and across doses, ezetimibe/simvastatin reduced LDL cholesterol significantly more than rosuvastatin [13]. Ezetimibe/simvastatin also produced significantly greater reductions in total cholesterol, non-HDL cholesterol and apolipoprotein B. Intensive lipid-lowering therapy with rosuvastatin 40 mg/day provided a greater LDL cholesterol-lowering effect than atorvastatin 80 mg/day, which enabled more patients to achieve their LDL cholesterol goals [13]. The EXPLORER study was designed to investigate the efficacy and safety of rosuvastatin 40 mg/day alone or in combination with ezetimibe 10 mg/day in patients with a high risk of coronary heart disease [14]. Interestingly, the combination of rosuvastatin/ezetimibe reduced LDL cholesterol significantly more than rosuvastatin alone. Other components of the lipid/lipoprotein profile were also significantly improved with rosuvastatin/ezetimibe. This combination therapy may have the strongest lipid-lowering effect.

The combination of ezetimibe/statin therapy reduced LDL cholesterol by 57% in familial hypercholesterolemia (FH) patients, regardless of the type of LDL receptor mutation. In clinical trials, ezetimibe/simvastatin produced greater reductions in LDL cholesterol than did monotherapy [15]. A possible molecular mechanism of the enhanced efficacy of ezetimibe plus simvastatin is decreased very (V) LDL and LDL apoB-100 concentrations through reduced VLDL production and the upregulation of LDL receptor-mediated LDL clearance. The additional decrease in plasma LDL cholesterol induced by ezetimibe showed wide inter-individual variability and was negatively correlated with the percent decrease in LDL cholesterol due to statin alone [16]. The reduction in LDL cholesterol in FH heterozygotes following combined therapy may affect the complex interplay between hepatic synthesis and the intestinal absorption of cholesterol. The usefulness of ezetimibe in enhancing the efficacy of apheresis therapy was evaluated in six Japanese patients with homozygous FH undergoing LDL-apheresis in combination with atorvastatin or simvastatin [17]. Thus ezetimibe also appears to be useful in combination with statins for FH patients.

Since diabetes mellitus (DM) patients have been shown to have more NPC1L1 mRNA than control subjects [18], ezetimibe may be useful for the treatment of patients with DM in whom cholesterol absorption may be upregulated. In patients with type 2 DM, combination therapy is usually required to optimize glucose metabolism as well as to help patients achieve aggressive targets for LDL cholesterol and other lipid parameters associated with cardiovascular risk. Ezetimibe/simvastatin therapy was effective and well tolerated under actual practice conditions in high-risk patients with coronary heart disease and/or DM [19]. In a randomized, double-blind, multicenter study in type 2 DM patients, LDL cholesterol was reduced significantly more by adding ezetimibe 10 mg/day to simvastatin 20 mg/day than by doubling the dose of simvastatin to 40 mg/day [20]. In addition, ezetimibe + simvastatin therapy also produced significant incremental reductions in non-HDL cholesterol, very LDL cholesterol and apolipoprotein B relative to simvastatin 40 mg/day.

Ezetimibe or ezetimibe/statin in combination with fibrate therapy

Although fenofibrate did not significantly reduce the risk of the primary outcome of coronary events, it did reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularizations in patients with type 2 DM [21]. Mixed hyperlipidemia is an important risk factor for the development of cardiovascular disease. Fenofibrate and ezetimibe offer complementary benefits to the lipid profile in patients with mixed hyperlipidemia. Patients in the fenofibrate plus ezetimibe and fenofibrate groups continued on their respective base study treatment, and patients in the ezetimibe and placebo groups were switched to fenofibrate plus ezetimibe and fenofibrate, respectively [22]. Fenofibrate plus ezetimibe produced significantly greater reductions in LDL cholesterol than fenofibrate alone. There were also significantly greater improvements in TG, HDL cholesterol, total cholesterol, non-HDL cholesterol, and apolipoprotein B with fenofibrate plus ezetimibe than with fenofibrate alone. In a multicenter, randomized, double-blind, placebo-controlled, parallel arm trial, the LDL cholesterol level was significantly reduced with ezetimibe/simvastatin + fenofibrate compared fenofibrate or placebo, but not compared

to ezetimibe/simvastatin [23]. HDL cholesterol and apolipoprotein A-I levels were significantly increased with ezetimibe/simvastatin + fenofibrate treatment compared to with ezetimibe/simvastatin or placebo. TG, non-HDL cholesterol, and apolipoprotein B levels were significantly reduced with ezetimibe/simvastatin + fenofibrate vs. all other treatments. Thus, the coadministration of ezetimibe/statin plus fenofibrate effectively improved the overall atherogenic lipid profile of patients with hyperlipidemia.

Genetic studies on ezetimibe therapy

The NPC1L1 gene may have naturally occurring coding mutations. These mutations might affect the response to ezetimibe among individuals who carry such mutants. In fact, three common single-nucleotide polymorphisms have been found in NPC1L1 (1735C > G [L272L], 25342A > C and 27677T > C [V1296]). Different NPC1L1 protein variants, such as Val^{55} to Leu^{55} and Ile^{1233} to Asp^{1233} have been found in a non-responder to ezetimibe [24]. In addition, 101 patients with primary hypercholesterolemia had a significantly greater reduction in plasma LDL cholesterol with ezetimibe than subjects with at least one copy of the haplotype. A detailed characterization of DNA variations in NPC1L1, the target of ezetimibe, demonstrated that common variants in this gene are significantly associated with the LDL cholesterol reduction in response to treatment with ezetimibe combined with a statin, but not with baseline LDL cholesterol [25]. Moreover, genetic variation in NPC1L1 contributes to the variability in cholesterol absorption and plasma levels of LDL cholesterol [26]. Rare variants identified in low-absorbers were found in 6% of 1832 African-Americans and were associated with lower plasma levels of LDL cholesterol. Although none of these common or rare variants have been confirmed, evidence has indicated an association between LDL cholesterol and NPC1L1 gene production as a target for ezetimibe.

Safety of ezetimibe

In 2382 patients with primary hypercholesterolemia, the coadministration of ezetimibe plus statin was well-tolerated [27]. In addition, in a randomized, double-blind, placebo-controlled trial, the safety and tolerability profiles for the ezetimibe/simvastatin and ezetimibe monotherapy groups were similar [28]. Ezetimibe plus statin therapy was well-tolerated and had a favorable safety profile in both male and female subgroups [29]. The coadministration of ezetimibe and statin was equally safe across specific age groups: age <65 vs. ≥65 years; age <75 vs. more than 75 years [30]. Simvastatin at doses up to 40 mg is a well-tolerated and effective therapy for children with heterozygous familial hypercholesterolemia [31]. In addition, the combination of fenofibrate plus ezetimibe was well tolerated during the extension study, with similar rates of ALT/AST elevations between fenofibrate plus ezetimibe and fenofibrate alone [22]. Overall, ezetimibe shows a favorable safety profile across all patients.

Conclusions

Ezetimibe is one of the most important medications for inhibiting cholesterol absorption. It has been shown to significantly reduce LDL cholesterol and improve other lipid parameters as either monotherapy or in combination therapy with other lipid-lowering medications, such as statins and fibrates. Such combination therapy is a more effective therapeutic option for the intensive lowering of LDL cholesterol. In addition, this therapy has been shown to have a favorable safety profile across all patients. Large randomized trials will be needed to evaluate the effectiveness of ezetimibe/statin or ezetimibe/fibrate therapy on clinical endpoints for the risk of coronary artery disease.

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